Pergamon

Tetrahedron Letters, Vol. 36, No. 13, pp. 2219-2222, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)00259-6

Catalytic Enantioselective Cyclopropanation with Bis(halomethyl)zinc Reagents. II. The Effect of Promoter Structure on Selectivity

Scott E. Denmark*, Beritte L. Christenson, and Stephen P. O'Connor

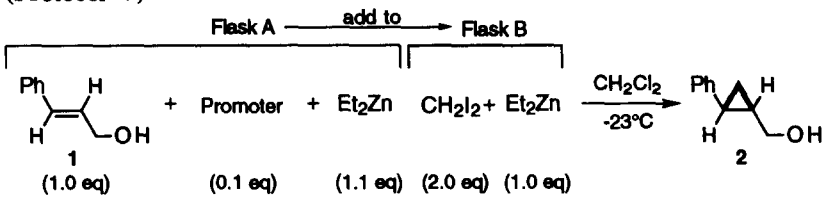
Roger Adams Laboratory, Department of Chemistry, University of Illinois, Urbana, IL 61801, USA

Key Words *: Cyclopropanation, allylic alcohol, bis(iodomethyl)zinc, chiral diamines*

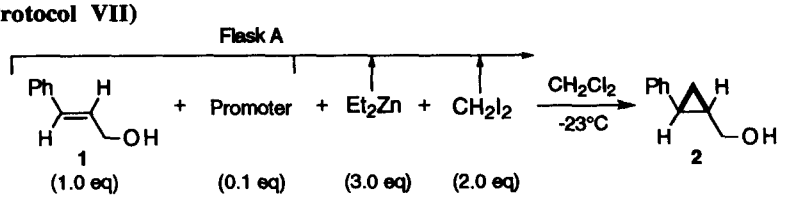
Abstract: *The catalytic, enantioselective cyclopropanation of cinnamyl alcohol has been accomplished with bis(iodomethyl)zinc in the presence of chiral bis(sulfonamides) derived from cyclohexanediamine. An extensive survey of diamine and sulfonamide structure has revealed a marked sensitivity to the spatial relationship of the amine groups, but only a modest dependence on the sulfonamide residue.*

In the preceding Letter, we described the optimization of an experimental protocol for the catalytic, enantioselective cyclopropanation of cinnamyl alcohol (**1**) with bis(iodomethyl)zinc in combination with bis(sulfonamide) derivatives of (*R,R*)-1,2-cyclohexanediamine.[1] It was found that the independent, pre-formation of an ethylzinc cinnamyloxide and the bis(iodomethyl)zinc reagent was crucial to obtain high and reproducible enantioselectivities. This was defined as Protocol V and is pictorially represented in Scheme I wherein the contents of flask A are added to flask B. A second protocol, employed in the earlier studies by Kobayashi,[2] involved the simultaneous, in-situ generation of these species by the sequential addition of the reagents as depicted in Scheme II. Using these two protocols, we have evaluated the importance of promoter structure on the rate and enantioselectivity of the cyclopropanation of **1** and disclose these studies in detail below.

Scheme I. (Protocol V)

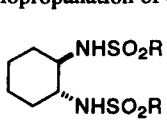


Scheme II. (Protocol VII)

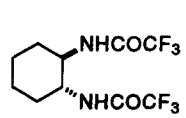


Each promoter was synthesized by the sulfonylation of the appropriate amine or diamine. Typically, the amine precursor was combined with 1.3 equiv (per amino group) of the appropriate sulfonyl chloride in the presence of 3 equiv of triethylamine (CH_2Cl_2 / 0 °C→rt).[3] The cyclopropanations were then performed using either of the protocols shown above. The progress of the reaction was monitored by GC and the enantiomeric excess **2** was determined by chiral HPLC analysis as described previously.

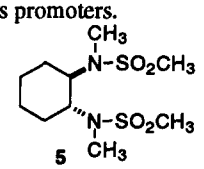
Table I. Cyclopropanation of cinnamyl alcohol under Protocol V with various promoters.



3



4



5

entry	promoter	protocol	R group	$t_{1/2}$, min[a]	e.e., %[b]
1	---	V		100	---
2	---	VII		200	---
3	**3a**	V	CH_3	50	80
4	**3a**	VII	CH_3	140	76
5	**3b**	V	CH_3CH_2	130	67
6	**3c**	V	$(CH_3)_2CH$	140	49
7	**3d**	V	CF_3	150	15[c]
8	**3e**	V	C_6H_5	70	75-77
9	**3f**	V	2,4,6-$(CH_3)_3C_6H_2$	140	32
10	**3g**	V	1-naphthyl	50	48
11	**3g**	VII	1-naphthyl	130	44
12	**3h**	V	4-NO_2-C_6H_4	70	76
13	**3h**	VII	4-NO_2-C_6H_4	150	74
14	**3i**	V	2-NO_2-4-CF_3-C_6H_3	70	63
15	**3i**	VII	2-NO_2-4-CF_3-C_6H_3	185	44
16	**3j**	V	4-$CH_3OC_6H_4$	60	74
17	**3k**	V	C_6F_5	100	29
18	**3k**	VII	C_6F_5	170	24
19	**4**	V		120	0
20	**5**	V		170	0

[a] Approximate time to 50 % conversion taken from a plot of the conversion from GC analysis.
[b] Determined by HPLC analysis on Chiralcel OJ column. [c] Opposite enantiomer of **2** was formed.

Since we[1] and Kobayashi[2] have found that sulfonamides derived from *trans*-1,2-diaminocyclohexane are effective promoters, we have first examined the influence of sulfonamide structure (**3a-3k**, **4**, **5**) in this framework. Table I contains the data for cyclopropanation with these compounds using both protocols. For comparison purposes, control experiments without promoters are also provided (entries 1, 2). For those promoters examined using both protocols (**3a**, **3g**, **3h**, **3i**, **3k**), both faster reactions and higher selectivities were obtained with Protocol V. The trend in entries 3-7 clearly shows the adverse effect of increasing bulk and

electronegativity of the residue in the aliphatic series, although the fluorine substitution may lead to anomalous behavior (vide infra). A similar trend was noted in the aromatic series, entries 8-11. While the phenyl derivative **3e** was a good promoter, the bulkier mesityl (**3f**) and 1-naphthyl (**3g**) derivatives led to slower and less selective reaction. Substituents of different electron demand (nitro, methoxy) when located in the para position were shown to have a negligible effect on the reaction (cf. entries 8, 12 and 16). However, a modest, and again unfavorable, steric effect was noted if the nitro group were located in the ortho position (entry 14).[4] As in the aliphatic series, the perfluoro derivative (**3k**) was significantly inferior in both catalytic activity and enantioselectivity (compare entries 8 and 17). The origin of the deleterious effect of fluorine substitution is unclear. We suspect that either the enhanced acidity of the NH groups or a zinc ligation by fluorine is responsible. Reactions in the presence of the trifluoroacetamide analog **4** and the *N,N'*-bis(methyl)bis(methanesulfonamide) derivative **5** were completely unselective.

The results with **3k** and **5** lead to the intriguing conclusion that the NH group on the sulfonamide must be present for the formation of the active catalytic species; replacement with zinc (if too acidic) or with methyl (by substitution), leads to inactive promoters. This conclusion is supported by preliminary NMR studies which clearly show that the NH protons (of **3a**) are still present after the addition of Et_2Zn at -23 °C. This suggests that coordination of the promoter by some zinc species (ZnI_2, $Zn(CH_2I_2)$ or EtZnOR) occurs though the sulfonamide oxygens.[5] This would be consistent with the lack of a significant electronegativity effect, though the magnitude of the steric effect is difficult to interpret. Indeed, the differences among **3a**, **3b** and **3h** become less pronounced when the optimum conditions[1] (Protocol V, 1.0 equiv ZnI_2, 0°C) were used: **3a** (<3 min, 86 % ee); **3b** (<3 min, 81 % ee); **3h** (<3 min, 78 % ee).

Having demonstrated the superiority of the methanesulfonamido group, we then turned our attention to the evaluation of framework structure. A variety of diamine skeleta as well as other mono and bifunctional promoters were examined using Protocol V and the results are compiled in Figure 1. To probe the role of skeletal flexibility, the 1,2-stilbenediamine-derived bis(sulfonamide) **6a** and the 1,3-diamino-1,3-diphenyl analog **7a** were examined. Neither of these compounds led to respectable levels of enantioselectivity. Furthermore, the failure of mono sulfonamides **9h**, **10a**, and **11**, even those bearing additional ligating groups clearly indicates the importance

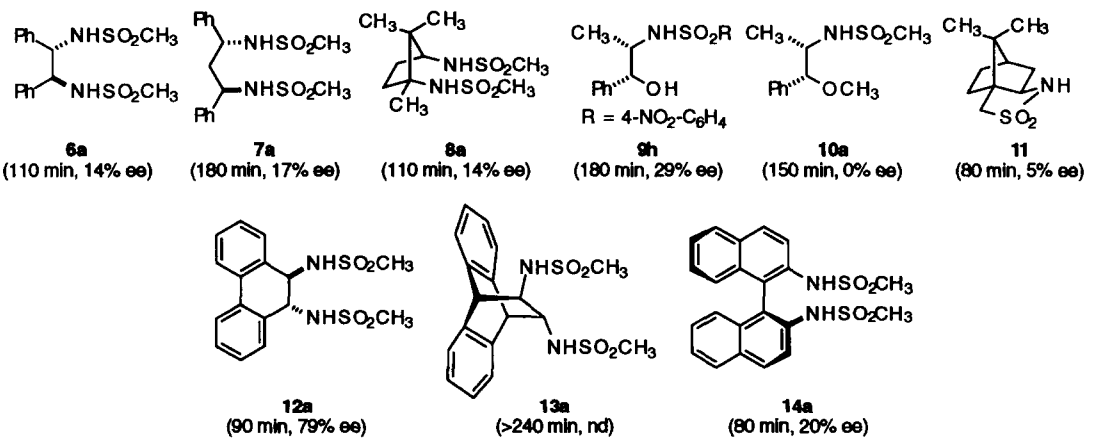
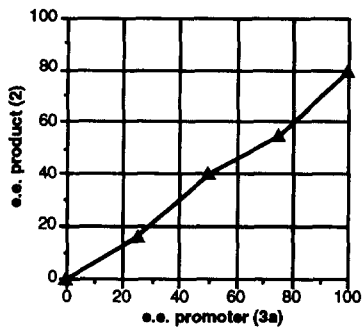


Figure 1. Structurally diverse promoters run under Protocol V ($t_{1/2}$, enantioselectivity).

of a chelating bis(sulfonamide) moiety. Closer refinement of the requirements for the spatial relationship of those chelating groups was assayed with the compounds **8a** and **12a-14a**. The 1,3-relationship found in **8a**, though rigidly defined is clearly not suitable, nor is a 1,4-relationship found in **14a** (dihedral angle ca. 90°). Of course, the steric encumbrance of the sulfonamide groups in **8a** or the acidity of those in **14a** may also be responsible for their poor performance. That the bis(sulfonamide) groups must behave cooperatively is clearly shown by the failure of the dibenzo[2.2.2]bicyclooctanediamine derivative **13a** in which the rigidly held dihedral angle of ca. 120° precludes normal chelation. The 9,10-phenanthrenediamine bis(sulfonamide) **12a** represents an intriguing hybrid between **3a** and **6a**. While maintaining a more fixed disposition of the amino groups at a similar dihedral angle, the aromatic "wings" are locked in a perpendicular orientation similarly to that found in **6a**[5] thereby enhancing the interactions of the sulfonamide groups with peri-hydrogens. Indeed, **12a** functioned as well as the best promoter (**3a**). Thus, it appears that a sterically unencumbered NH-bis(sulfonamide) with rigidly held amino groups *capable of chelation* with a 60-75° bite angle is required to generate the asymmetric catalyst.

Finally, we have also demonstrated a linear relationship between the e.e. of the promoter (**3a**) and the e.e. of the cyclopropanemethanol product **2** using Protocol V. This supports the notion that (1) only one promoter molecule is present in the stereochemistry determining transition state and (2) the resting state of any promoter-zinc complex is monomeric or dissociates with low activation.



In conclusion, we have identified some of the characteristics of a promoter for the catalytic, asymmetric cyclopropanation of allylic alcohols using bis(iodomethyl)zinc. To date the most effective promoter in terms of reaction rate and enantioselectivity is the simple bis(methansulfonamide) of 1,2-cyclohexanediamine. More flexible diamines or those not capable of achieving a chelate bite angle of ca. 60° are not as effective. Larger or strongly acidifying sulfonamide groups lead to poorly selective reactions. Future studies on the nature of the catalytically active species and the scope of the reaction are in progress.

Acknowledgment: We are grateful to the Upjohn Company for financial support. BLC thanks the Wenner-Glen Center Foundation for a fellowship. SPO thanks the University of Illinois for a Graduate Fellowship (DOE).

REFERENCES AND NOTES

(1) Denmark, S. E.; Christenson, B. L.; Coe, D. M.; O'Connor, S. P. preceding Letter in this issue.

(2) (a) Kobayashi, S.; Takahashi, H.; Yoshioka, M.; Ohno, M. *Tetrahedron Lett.* **1992**, *33*, 2575. (b) Kobayashi, S.; Takahashi, H.; Imai, N. *Chem. Lett.* **1994**, 177. (c) Kobayashi, S.; Takahashi, H.; Imai, N.; Sakamoto, K. *Tetrahedron Lett.* **1994**, *35*, 7045.

(3) All promoters were fully characterized (^{1}H and ^{13}C NMR, IR, MS, $[\alpha]_D$, CHN).

(4) Kobayashi has noted a similar trend in the behavior of the 2-, 3-,. and 4-nitrobenzenesulfonamides.

(5) An X-ray crystallographic analysis of a methylaluminum complex of **6d** is dimeric in the solid state and shows chelation of the aluminum by the nitrogens, and bridging through the oxygens. Corey, E. J.; Sarshar, S.; Bordner, J. *J. Am. Chem. Soc.* **1992**, *114*, 7938.

(*Received in USA* 10 *January* 1995; *revised* 26 *January* 1995; *accepted* 2 *February* 1995)